**Institution: University College London**

**Unit of Assessment: 11 – Computer Science and Informatics**

**Title of case study: Improving prostate cancer diagnosis and care using computer simulation and medical image registration**

## 1. Summary of the impact

UCL's research has led to changes in patient care for men with prostate cancer, through the implementation of less invasive, image-directed treatment and diagnostic strategies, and clinical trials that use these techniques. The use of medical image registration software to deliver high-intensity ultrasound therapy in a targeted manner has been shown to change the treatment plan in half of the patients participating in a clinical study. New biopsy criteria are now used routinely to classify patient risk at University College Hospital, where, since 2009, clinicians have determined the treatment options for more than 741 prostate cancer patients. The scheme has been adopted, by 15 other hospitals in the UK and internationally, where it has become the recommended standard of care, and has been used to treat more than 1,200 patients.

## 2. Underpinning research

Dr. Barratt is an academic member of the UCL Centre for Medical Image Computing. His field of expertise includes medical image analysis, especially medical image registration, image processing, and computational modelling of soft-tissue organ motion and surgical procedures for the prediction and compensation of organ deformation in image-guided surgery systems. He has also applied computational modelling to investigate the expected efficacy of new surgical techniques. A key insight arising from the research he has conducted since 2007 is that three-dimensional (3D) computational models of soft-tissue and surgical instrument motion provide a powerful tool for solving conventionally challenging image registration problems in which structures move and deform between images. Such models also provide a powerful tool for simulating surgical procedures for the purposes of developing new clinical protocols to implement and interpret the results of those procedures. Specifically, statistical shape models that represent *subject-specific* variation in organ shape, for example, due to physical deformation when in contact with a surgical instrument, provide physically constrained representations that are helpful in regularising deformation fields computed by image registration algorithms.

In Dr. Barratt's research, two novel approaches have been developed in close collaboration with clinicians at University College Hospital (UCH) [1-3]:

Firstly, computational biomechanics (finite-element analysis) has been used to simulate organ deformations, given a static 3D mesh representation derived from a medical image. The resulting deformed shapes are used as synthetic training data for building a statistical shape/motion model. This approach is particularly useful for applications where the organ deformation cannot be quantified using imaging in advance, either because quantifying this deformation using imaging is not feasible or too expensive, or when physical deformations are due to instruments only used at the time of surgery. In such cases, prior information in the form of a pre-built 3D deformable organ model enables deformations to be predicted much more rapidly than applying finite-element methods directly. Potential problems of numerical instability and determination of boundary conditions from typically poor-quality intraoperative images are also avoided.

Secondly, an algorithmic framework has been developed for registering deformable geometric organ models (for example, represented by a triangulated mesh) directly to images of the same organ. Again, this approach is particularly useful for surgical applications where a simplified, easy-to-interpret geometric representation of the organ of interest is ideal for surgical planning and transferring salient clinical data between different clinical teams. Models typically contain only information that is surgically relevant, such as tumour size, shape and location, and can be visualised easily using standard graphics hardware. Much of Dr. Barratt's research has focused on applying this approach to problems in prostate cancer biopsy and therapy, utilising patient-specific statistical shape/motion models of the prostate generated from magnetic resonance imaging (MRI) data [1-3].

The clinical motivation for this work is problems encountered when attempting to validate and implement clinically an *MRI-directed* approach to prostate cancer diagnosis and treatment. In this

approach, pathological and anatomical information from MRI images of the prostate obtained prior to a surgical procedure are used to plan and guide the procedure by superimposing a graphical representation of MRI-visible tumours onto real-time ultrasound images obtained during the procedure for the purposes of guidance. This overcomes the current limitation that most prostate tumours are not visible in ultrasound images and therefore targeting them is highly challenging without computer assistance. It also provides a cost-effective and accessible alternative to performing surgical procedures within an MRI scanner (i.e. under MRI guidance), which is prohibitively expensive and currently only available in a small number of centres across the world.

As the research outlined above developed, and MRI-directed prostate needle biopsy applications were explored, further research was undertaken to apply computer modelling methods to simulate the biopsy procedure and to develop new criteria for estimating tumour burden (i.e. volume). This work involved the development of computer models of needle insertion, based on anatomical information obtained from pelvic MRI images, that included physical effects such as needle bending and image registration errors (estimated from work undertaken in other parts of the research programme as well as from the results of other research groups). Detailed 3D geometric computer models of the prostate, including tumour size, shape and location, were reconstructed automatically from images of surgically excised prostate specimens using software developed by Dr. Barratt's research group. The software used image processing, combined with image registration, to detect tumour regions and re-orientate consecutive histological images [1-3].

Three computer simulation studies were carried out between 2010 and 2012 to:

i) devise new criteria for estimating tumour burden from transperineal, template-guided biopsy samples [4];
ii) compare different biopsy strategies for the detection of clinically important cancer (i.e. cancer that requires treatment) [5]; and
iii) investigate and highlight issues associated with tumour-targeted biopsy, including the proposition of example new criteria, derived from computer simulations [6]. These studies are closely linked with the application of novel image registration techniques developed as part of the core research activity [1-3]. Such criteria are vitally important for patient management, since they dictate the treatment options available to patients as a result of undergoing this procedure.

These computer simulation studies involved predicting the cancer core length of tissue sample - i.e. the length of cancerous tissue in millimetres - for different biopsy schemes, using 3D computer reconstructions from a historical database of histopathological images of a step-sectioned prostate specimens. The simulations took account of various sources of error, such as needle deflection, that can arise during a biopsy, and provided data for a statistical analysis from which cut-off criteria were determined to estimate disease burden.

***Key researchers:*** Dr Dean Barratt, Senior Lecturer (2007 – present); Dr. Yipeng Hu – Research Assistant and part-time PhD student (Oct 2007 – Sep 2012); Research Associate (Oct 2012-present); Dr. Tim Carter – Senior Research Associate (July 2009 – Sep 2011); Dr. Steven Thompson – Research Associate (Jan - Oct 2012); Professor David Hawkes – Professor of Imaging Science and Director of the UCL Centre for Medical Image Computing (2007- present)

**3. References to the research**


1. Hu Y, Ahmed HU, Taylor Z, Allen C, Emberton M, Hawkes DJ, Barratt DC. *MR to ultrasound registration for image-guided prostate interventions*. Med Image Anal 2012;16(3):687-703. DOI: doi.org/c5bxqj
2. Hu, Y., Carter, T. J., Ahmed, H. U., Emberton, M., Allen, C., Hawkes, D. J., & Barratt, D. C. Modelling Prostate Motion for Data Fusion During Image-Guided Interventions. IEEE Transactions on Medical Imaging 2011; 30(11), 1887–1900. DOI: doi.org/bt2m6m
3. US Patent US20120155734 A1: Hu Y, and Barratt DC. *Apparatus and method for registering two medical images*. Filed: Aug 2010; Published: Jun 2012; Granted: Sep 2013. http://assignments.uspto.gov/assignments/q?db=pat&pub=20120155734
4. Ahmed HU, Hu Y, Carter T, Arumainayagam N, Lecornet E, Freeman A, Hawkes D, Barratt

DC, Emberton M. *Characterising Clinically Significant Prostate Cancer using Template Prostate Mapping Biopsy*, J Urol. 2011; 186(2): 458-464. DOI: doi.org/bkr26v

5. Hu Y, Ahmed HU, Carter T, Arumainayagam N, Lecornet E, Barzell W, Freeman A, Nevoux P, Hawkes DJ, Villers A, Emberton M, Barratt DC*, A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy.* BJU Int 2012; 110 (6) 812 – 820. DOI: doi.org/n6w
6. Nicola L. Robertson, Yipeng Hu, Hashim U. Ahmed, Alex Freeman, Dean Barratt, Mark Emberton*, Prostate Cancer Risk Inflation as a Consequence of Image-targeted Biopsy of the Prostate: A Computer Simulation Study,* European Urology (In Press Jan 2013) doi.org/n6x

References 1, 2, and 6 best demonstrate research quality as these are published in leading journals in the field of medical image computing and urology.

Since 2006, this work has received almost £5 million from engineering funding schemes aimed at applied research. Funders included the EPSRC, the Royal Academy of Engineering, NHS NIHR, the Wellcome Trust, and the Department of Health.

## 4. Details of the impact

Prostate cancer is the most common male cancer in the UK, many countries in Europe, North America, and Australasia. The disease is a leading cause of cancer-related death in the western world.

Dr. Barratt's development of novel criteria for diagnosing prostate cancer from computer modelling of needle biopsy has been of benefit to clinicians, men suspected of having prostate cancer, and men already diagnosed with the disease who require a comprehensive assessment of the extent and type of their disease prior to treatment. As a result of this research, **clinicians now have access to clinical tools** for implementing and validating MR-directed prostate biopsy as well as tools for accurately classifying patient risk and determining viable treatment options [a,b]. **Patients directly benefit** from this research through the **significant improvement in accuracy of needle biopsy investigations**, which in turn provides **greater confidence when deciding between different treatment options** [a,b].

**Development and adoption of clinical tools:** From 2007 onwards, Barratt's collaboration with clinicians at University College Hospital (UCH) led to new clinical criteria for image-directed biopsy using computer modelling of this procedure. For transperineal, template-guided biopsy mapping, these **criteria were quickly adopted into clinical practice at UCH and from September 2009, applied to all patients undergoing this procedure,** whether or not the patient was a volunteer within a clinical trial [b]. The criteria were also incorporated within an intuitive and easy-to-understand **clinical classification scheme** that also includes histological information on the aggressiveness of disease, measured by the so-called Gleason Grade. This scheme, commonly known as the "Traffic Light Scheme" and developed by clinicians in collaboration with Dr Barratt's team, provides a highly visual way of documenting patient risk by using a colour-coded system that is easily recognisable to patients. It has been found to be particularly useful during patient consultations as a means of allowing the patient to see where the burden of disease is and to **make an informed choice**, together with the clinician, about which treatment option to pursue [a,b].

Since its introduction as part of the routine clinical protocol at UCH in 2009, the Traffic Light scheme for classifying prostate cancer risk has **determined the treatment options offered to more than 741 men with the disease** who underwent a template-guided biopsy mapping before 31 July 2013 [b]. This includes men treated under the NHS and privately both outside and inside ongoing clinical trials; the results of this test are often used to determine eligibility for clinical trials. The scheme is also used as part of the protocol of a major 3-year NHS/NIHR-sponsored Health Technology Assessment trial, the PROMISE trial, which began recruiting in 2012 and currently includes four centres in the UK. The aim of this study is to evaluate the clinical efficacy of MR in the diagnosis and characterisation of prostate cancer in a hospital setting in England and Wales. The trial has recruited 50 patients so far.

The **scheme was adopted by 15 centres in the UK and internationally between 2008 and 31 July 2013**, including The Royal Marsden, St. Mary's (London), Bristol, Basingstoke and the Whittington Hospital, with plans for it to be introduced into all nine hospitals in the London Cancer Network by 2014. In Europe, the scheme is now used in hospitals in Zurich and Lausanne in Switzerland. The current estimate of the total number of patients whose treatment has been determined by this scheme is in excess of 1,200.

As a further indication of the impact of this research on medical practice, a recent review of prostate cancer diagnosis [c], published in the influential British Medical Journal, also recommends that new biomarkers should be validated against the thresholds employed in this scheme, citing [output 4, above]. It is also anticipated that the scheme will be **included as part of the national guidelines issued by the Royal College of Pathologists**, which is currently under development and is due to be published in 2014 [b].

**Patient benefits:** The MR-directed biopsy outlined above enables biopsy sampling that is sufficiently accurate for tumours to be targeted selectively. In this approach, tissue samples are collected only from regions that appear to be tumours in the MR images, which makes the **procedure more efficient, more accurate, less invasive (and therefore posing a lower risk of infection), and cheaper compared with established biopsy techniques**.

**Clinical trials:** The image registration software that implements the techniques described in Section 2 is being used for targeted biopsy and therapy as part of two clinical trials. In one trial, the surgical value of using this software in an initial series of 24 patients was analysed [d]. The results indicate that the use of the software to determine precisely where an MRI-visible tumour is located within ultrasound images obtained during the high-intensity focused ultrasound (HIFU) therapy led to **a change in the surgical plan, determined using the standard clinical method, in half of the patients**. In these patients, the **size of the treated region was increased** to ensure that the tumour was fully ablated. Clinical follow-up data are not yet available, but the longer-term impact of employing this technology is that the **treatment is more effective** than it would have been if performed using standard clinical methods in a substantial proportion of patients.

To date, in fifty patients who went on to be treated using minimally invasive, MR-directed therapy within a clinical trial and as a result of criteria, the therapy was delivered using the image registration technology developed in this research [a]. The clinical experience with these patients is being used as evidence of clinical safety and efficacy as part of a submission for CE marking a commercial medical device that incorporates this technology.

**5. Sources to corroborate the impact**

[a] A support letter from a Professor of Interventional Oncology at UCH corroborates that the key technologies described here have been translated into clinical practice and provide an important new clinical tool for prostate cancer diagnosis and treatment. Available on request.

[b] Supporting statement from the Lead Urological Pathologist at UCH corroborates that the output of the computational prostate biopsy modelling studies has led to new diagnostic criteria that are now applied as part of routine clinical practice at UCH and other hospitals, has had a positive impact on the decision making of a multidisciplinary clinical team since being introduced, and is due to be considered for inclusion in the Royal College of Pathologists national guidelines. Available on request.

[c] Corroboration of the clinical need for new criteria that take into account new image-directed approaches to diagnosing prostate cancer is on page 3 of Wilt, T. and Ahmed, H.U. Prostate cancer screening and the management of clinically localized disease. BMJ 2013; 346. doi.org/n62

[d] Corroboration of the observation that introducing MRI-ultrasound image registration/fusion software changes to the surgical plan of approximately half of patients undergoing localised HIFU therapy for prostate cancer is on page 1 of Dickinson, L., Hu, Y., Ahmed, H. U., Allen, C., Kirkham, A. P., Emberton, M., & Barratt, D. (2013). Image-directed, tissue-preserving focal therapy of prostate cancer: a feasibility study of a novel deformable magnetic resonance-ultrasound (MR-US) registration system. *BJU international*, *112*(5), 594–601. DOI: doi.org/n6z